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DEPARTMENT OF THE ARMY  
Fort Detrick  
Frederick, Maryland

BEHAVIOR OF THE RETICULOENDOTHELIAL SYSTEM  
IN EXPERIMENTALLY-INDUCED ANTHRAX

[Following is a translation of an article by Stefano Marradi Fabroni of Clinica del Lavoro (Industrial medicine clinic) of the University of Milan, Italy, in the Italian-language publication, La Medicina del Lavoro (Industrial medicine), Vol. 25, pp. 379-383 (1934)].

The interesting research which has been published in recent years [Translator's note: ante-1934] in Germany, Italy and France on the reticuloendothelial system has brought to light the important contribution made by it in various hematopoietic, metabolic and erythrocytolytic functions. This research has also indicated how several still unsolved problems of miltiridatism and problems associated with immunity must be attributed to this system.

If, however, we were to try to summarize all the various attempts at exploration of this system, we would be obliged to bring to the fore a wide diversity of uncertain conclusions. Such results, which at first sight might seem even contradictory or paradoxical, must surely have an important significance of their own, indicating the multiplicity of activities which are strengthened or augmented by the reticuloendothelial system, identified as that mesenchymal residual tissue scattered so widely throughout the body tissues and which has not undergone morphological differentiation, but which represents an organic defense reserve. This highly important defense reserve is called upon by the organism whenever it finds itself threatened or attacked by any pathological condition.

This organic substrate, working in perfect harmony with the organism, remains in an embryonic state and its differentiation works rather gradually whenever it is stimulated by organic necessity; this explains its operation in infectious conditions by phagocytosis with intracellular neutraliza-

tion of toxins and the production of antibodies. It also plays a definite and decisive role in cellular and humoral (body-fluid) immunities.

Most scholars have attempted to delineate the anatomical and physiological limits of the reticuloendothelial system with the aid of so-called "blocking", a method whereby specific powers of the reticuloendothelial system are stopped or inhibited; this method of investigation, although possible theoretically, offers insuperable obstacles to its practical achievement because (1) the amount of any colloid used taken up by the reticuloendothelial system will depend strictly on the fineness of the colloidal micelle; (2) because it is so difficult to sensitize the reticuloendothelial system at all levels and (3) above all else, because the manner in which the colloid is introduced, the quantity of colloid, the rate at which it is added and the kind of colloid used, whether organic or inorganic, will at times induce the reticuloendothelial system to reduce its specific powers and, at other times, will act to render its specific powers non-functional.

The author recently carried out several investigations (1) to this end, leading him to conclude that the introduction into the organism of a colloidal substance capable, as is known, of becoming fixed to the cells of the reticuloendothelial system, constitutes a stimulus to the reticuloendothelial system's cells inducing a state of higher resistance to the action brought about by the secondary, subsequent introduction of salts of heavy metals and since there is, in addition, an optimum action of such a stimulus, the resistance once again starts to drop off beyond some point.

The investigations which are the subject of this paper were carried out using identical stimulation therapy though with three different colloids and their purpose was to determine whether the increase in allergy and resistance thus obtained could be made to show themselves in the organism's reaction against additional provocation induced by an infectious condition (anthrax).

In these investigations, too, the author used rabbits for his experiments and he divided them into three separate groups according to the type of colloid which was injected. Each group was further subdivided into two subgroups; the first of the two subgroups was a control group left untreated with stimulating substances before they were inoculated with anthrax. The second subgroup, on the contrary, was given preliminary intravenous injections containing for the first main group a solution of 1 ml. of 2% silver protein in a

physiological solution, for the second main group milk and for the third group colloidal iodine.

The anthrax inoculation was carried out by subcutaneous injection of a suspension of germs in an inoculating loop.

Every three days from the time of inoculation the author gave these animals an intravenous injection of the same amount of the colloid to reinforce the stimulative action. The results obtained are given in the following tables:

TAVOLA I. (a)

Coeligi	Iniezione di Latte (b)	Dopo 24h;	48h;	72h;	96h;	120h; (c)
1	Controllo (d)					+
2	Controllo					+
3						+
4						+
5						+
6						+
7						+
8						+
9						+
10						+

INOCULAZIONE DEL CARBONCHIO (e)

Table 1 legend

- (a) Table 1
- (b) Rabbits injected with milk
- (c) After 24 hrs., 48 hrs., 72 hrs., 96 hrs., 120 hrs.
- (d) Control
- (e) Inoculation with anthrax

TAVOLA II. (a)

Conigli	Iniezione di Collargolo	Dopo 24h:	48h:	72h:	96h:	120h:
1	Controllo (d)					
2	Controllo					
3	Controllo					
4	Controllo					
5	Controllo					
6	+++					
7	+					
8	+++					
9	+					
10	+					
11	+					
12	+++					
13	+++					
14	+++					
15	+					

INOCULAZIONE DEL CARBONCHIO (e)

**Table 2 legend**

- (a) Table 2
- (b) Rabbits injected with silver protein
- (c) After 24 hrs., 48 hrs., 72 hrs., 96 hrs., 120 hrs.
- (d) Control
- (e) Inoculation with anthrax

TAVOLA III (a)

Controlli	Iniezione di Iodio colloidale (b)	Dopo 24h	48h	72h	96h	120h (a)
1	Controllo (d)					+
2	Controllo					+
3	++1					+
4	++1					+
5	++1					+
6	++1					+
7	+					+
8	+					+
9	+					+
10	+					+

INOCULAZIONE DEL CARBONCINO (e)

Table 3 legend

- (a) Table 3
- (b) Rabbits injected with colloidal iodine
- (c) After 24 hrs., 48 hrs., 72 hrs., 96 hrs., 120 hrs.
- (d) Control
- (e) Inoculation with anthrax

The tables given above present sufficient evidence of the fact that the reticuloendothelial system on being adequately stimulated, is capable of increasing the body's organic powers of defense against toxic action by metal salts, but the reticuloendothelial system does not behave in the same way against anthrax infection. On close examination it would seem rather that the powers of defense reacted even more inadequately in those animals whose reticuloendothelial systems had been previously stimulated, than in the cases of the control animals.

In fact, in those experiments where silver protein or milk were used, none of the animals treated resisted more than the control animals to invasion by septicemia and only those which had been previously sensitized by colloidal iodine showed any modest increase in resistance.

We do not believe, however, that one need attribute this fact to any effective protective action on the part of the reticuloendothelial system, but that perhaps it was rather due to the antitoxic, bactericidal action of the colloidal iodine micelle, picked up and carried on by the phagocytal

elements which in this way would have found an aid in carrying out their phagocytal, bacteriolytic function.

On the whole then we should try to explain the reasons for the reticuloendothelial system's failure to carry out a defensive, protective action against anthrax infection, even though it had been previously acted upon by an adequate stimulus capable of increasing its powers of response.

Because of this it is necessary to consider how it is that the monocytes appear considerably increased in the circulation following this stimulus, whereupon the first phase of reticuloendothelial reaction begins. These elements, powerful macrophages, seem to begin to carry out their tasks as soon as the anthrax inoculation is given, but in our case the bacteriolytic phase failed to appear due to the resistance offered by the germs, which survived. This explains how the germs, englobed only by monocytes, were transported by them and rapidly disseminated throughout the entire organism, frustrating every further defensive action on the part of the organism and thereby establishing the clinical picture of septicemia.

It can be decisively stated that the protective and defensive action which we succeeded in inducing in the reticuloendothelial system and which was supposed to limit and overcome the infectious process, showed itself to be inadequate to the resistance and toxic infectiousness of the germ and, moreover, was actually converted into a means for more rapid dissemination of the germs. This would also explain the greater resistance to infection shown by the control animals which, not having been previously stimulated, showed themselves to be at the moment of inoculation less equipped with those elements or factors which, in our case, instead of protecting the animal, were reduced to means by which the germs could be disseminated.

We believe we can assume that the reticuloendothelial system reacted to the previously induced stimulus, increasing its defensive powers. These powers must not be taken as being in any sense absolute because, as we have seen, they are held within biological and biodynamic limits beyond which the defensive action is canceled out if not actually converted into actual serious damage.

#### SUMMARY

In a series of 35 experiments carried out on rabbits the author first sensitized the reticuloendothelial system by parenteral injection of colloidal substances (silver, milk and iodine). The animals were subsequently inoculated with anthrax.



It was noted that the state of allergy and resistance induced by the stimulating action on the reticuloendothelial system did not make itself felt against anthrax infection, while it seemed, instead, that the defensive powers reacted more ineffectively in sensitized animals than in control animals.

The author believes that these results are attributable to the fact that the monocytosis induced by the stimulating action on the reticuloendothelial system represents a barrier which can easily be overcome by the infectious power of the anthrax germ so that these germs, resisting the phagocytal and bacteriolytic action of the monocytes, would be englobed by the monocytes, carried along by them and distributed throughout the body in a live state, thereby speeding up and aiding the actual spread of septicemia.

#### REFERENCE

(1) Fabroni S.M., "The reticuloendothelial system in defense of the organism against the salts of heavy metals." Haematologica, Vol. X, No. I, 1929.

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